

Wnt3a reestablishes osteogenic capacity to bone grafts from aged animals.

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Authors: Philipp Leucht, Jie Jiang, Du Cheng, Bo Liu, Girija Dhamdhere, Mark Yang Fang, Stefanie D Monica, Jonathan J Urena, Whitney Cole, Lane R Smith, Alesha B Castillo, Michael T Longaker, Jill A Helms

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Public Summary:

Age-related degeneration of the bone marrow contributes to delayed fracture-healing and osteoporosis-related fractures in the elderly. The mechanisms underlying this degeneration are unknown, but they may relate to the level of Wnt signaling, a type of hormone, within the aged bone marrow. Engineered mice were used in conjunction with bone-grafts to follow the fates of cells involved in the engraftment. Cells in the bone graft demonstrated seemed expressed fewer bone-forming genes and more fat-forming genes. This age-related fat-forming shift was accompanied by reduced Wnt signaling and a loss in bone-forming potential. In both large and small animal models, bone-forming potential was restored to aged bone grafts by addition of the hormone Wnt3a. We developed an effective, clinically applicable, regenerative medicine-based strategy that has the potential to revitalize bone grafts in aged patients.

Scientific Abstract:

BACKGROUND: Age-related fatty degeneration of the bone marrow contributes to delayed fracture-healing and osteoporosis-related fractures in the elderly. The mechanisms underlying this fatty change are unknown, but they may relate to the level of Wnt signaling within the aged marrow cavity. **METHODS:** Transgenic mice were used in conjunction with a syngeneic bone-graft model to follow the fates of cells involved in the engraftment. Immunohistochemistry along with quantitative assays were used to evaluate Wnt signaling and adipogenic and osteogenic gene expression in bone grafts from young and aged mice. Liposomal Wnt3a protein (L-Wnt3a) was tested for its ability to restore osteogenic potential to aged bone grafts in critical-size defect models created in mice and in rabbits. Radiography, microquantitative computed tomography (micro-CT) reconstruction, histology, and histomorphometric measurements were used to quantify bone-healing resulting from L-Wnt3a or a control substance (liposomal phosphate-buffered saline solution [L-PBS]). **RESULTS:** Expression profiling of cells in a bone graft demonstrated a shift away from an osteogenic gene profile and toward an adipogenic one with age. This age-related adipogenic shift was accompanied by a significant reduction ($p < 0.05$) in Wnt signaling and a loss in osteogenic potential. In both large and small animal models, osteogenic competence was restored to aged bone grafts by a brief incubation with the stem-cell factor Wnt3a. In addition, liposomal Wnt3a significantly reduced cell death in the bone graft, resulting in significantly more osseous regenerate in comparison with controls. **CONCLUSIONS:** Liposomal Wnt3a enhances cell survival and reestablishes the osteogenic capacity of bone grafts from aged animals. **CLINICAL RELEVANCE:** We developed an effective, clinically applicable, regenerative medicine-based strategy for revitalizing bone grafts from aged patients.

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